Audiência Pública sobre Hepatites Virais: Novas terapias hepatite C

Brasília 08 de maio de 2014

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- Membro do Comitê Assessor de Hepatites do MS
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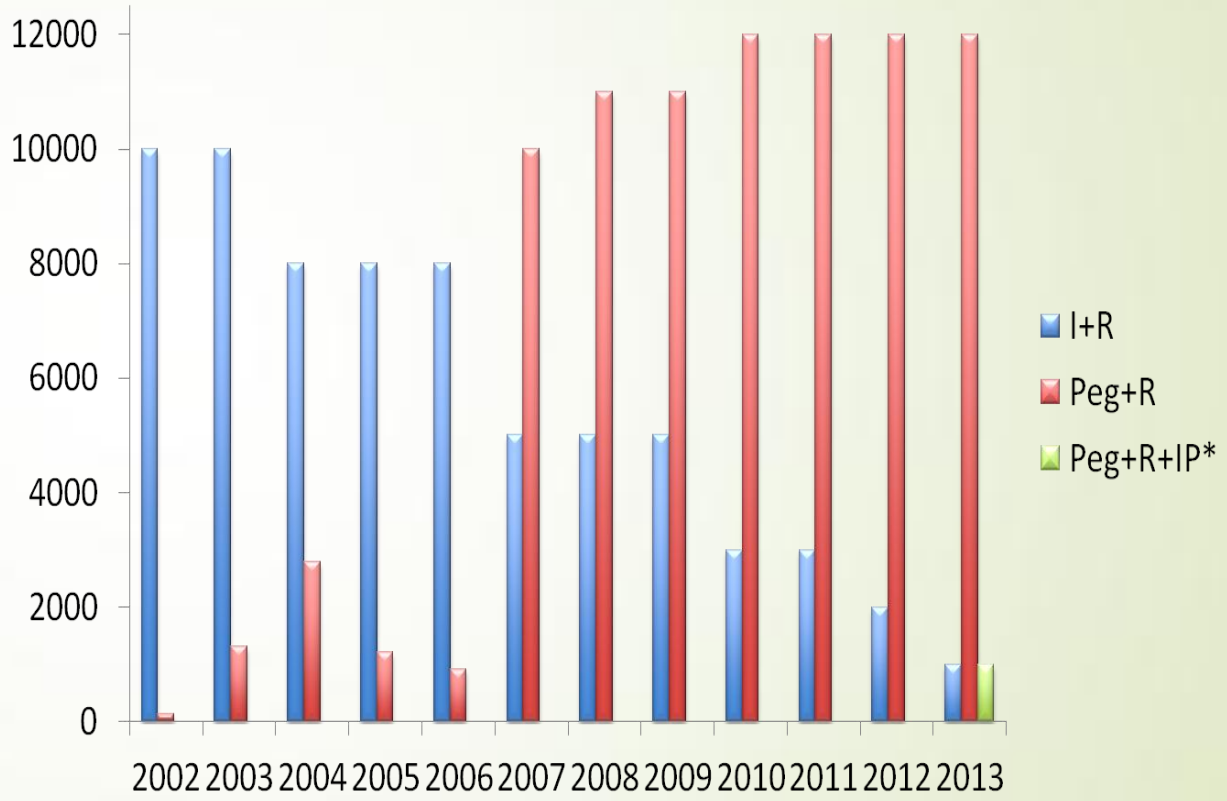
- Membro do Comitê de Hepatites da Sociedade Brasileira de Infectologia
- Presidente da Comissão Permanente de Higiene e Saúde da Câmara de Santos

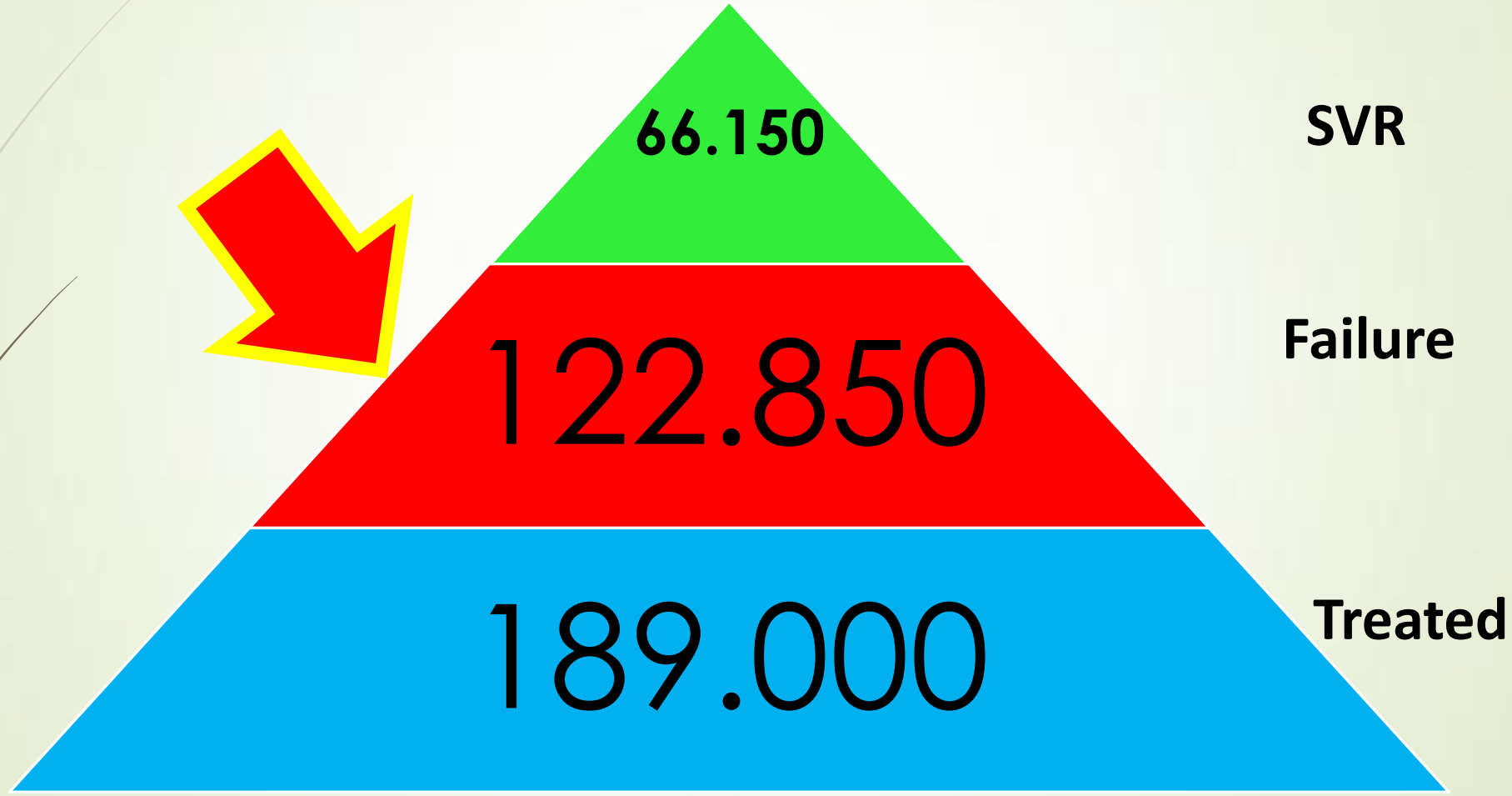
Estimated Percentage of Patients Diagnosed, Treated and type of therapy in Brazil.

- Brazil (2007):
  - Diagnosed ~ 10%
  - Treated ~ .79%



Kershenobich D et al. Liver Intl., 2011.
Adapted Datasus

Low SVR rates in real life settings (~30%)
2002 - 2012: need to improve!

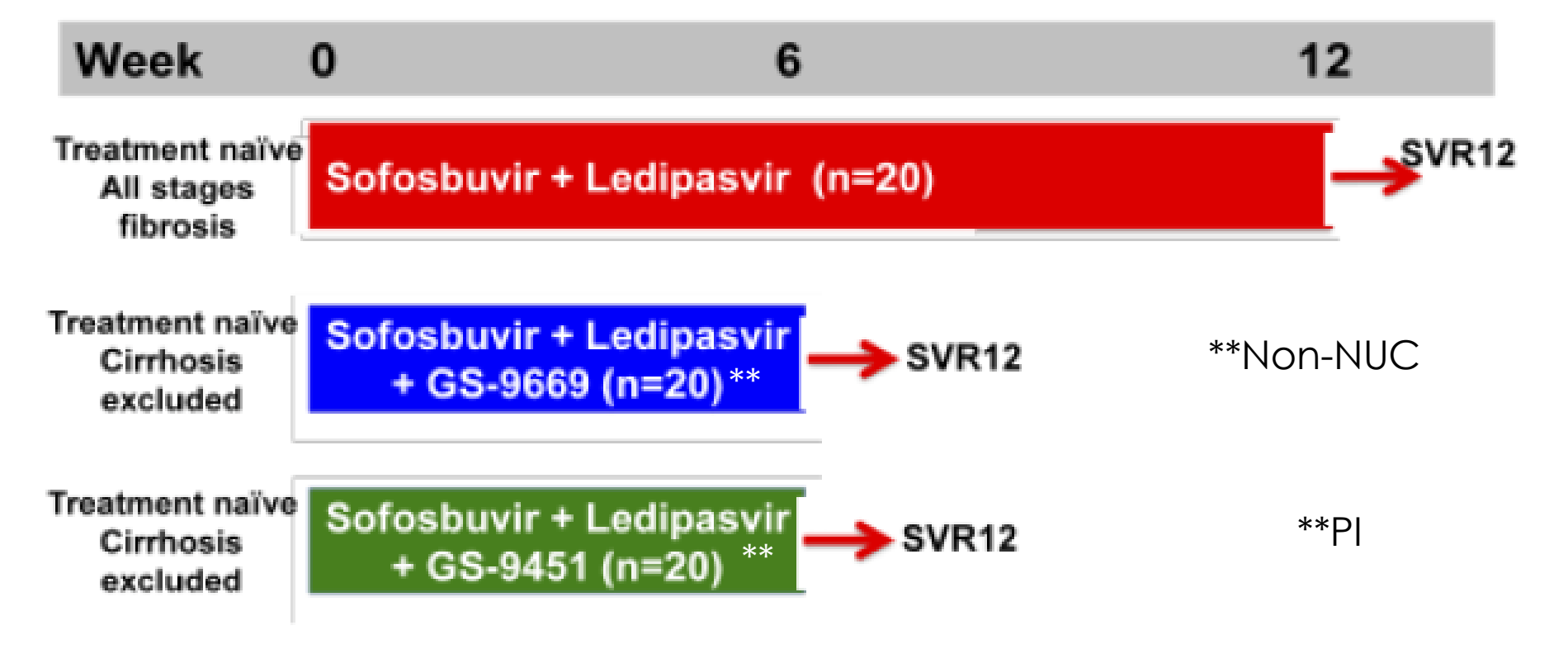


Adapted Datasus

But…what really matters?
Is it possible to change??

Sinergy Trial (NIH Study): design

Hard to treat population*, all oral, short duration, naïve.

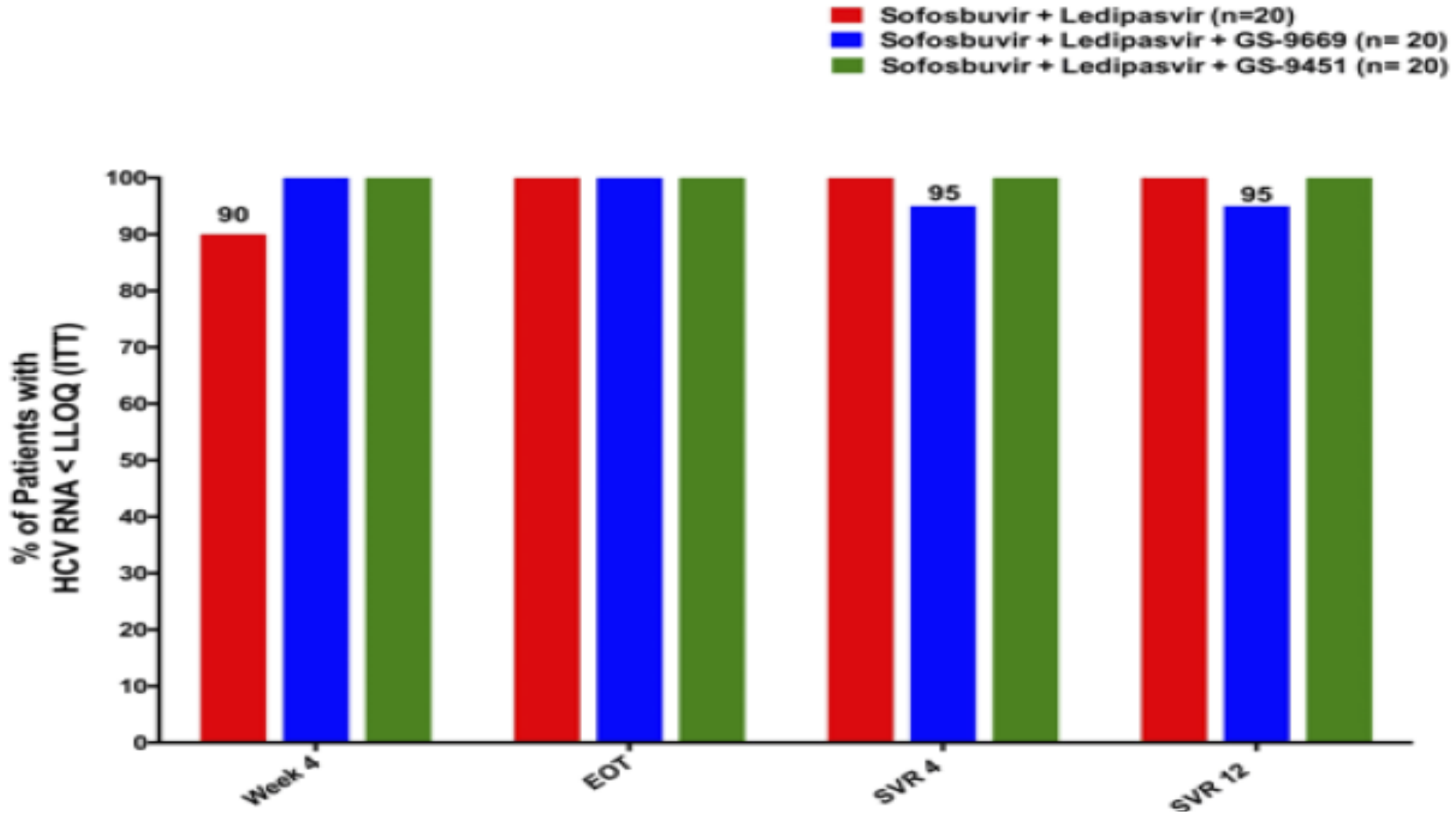


*** 88% African-American, 72% male, 70% genotype 1a, 70% high viral load, 82% non-CC haplotype, 25-35% > F3**

http://www.natap.org/2014/CROI/croi_110.htm

Sinergy Trial (NIH Study): results.

Figure 26: SYNERGY (NIH trial): Treatment response (ITT)



No side effects, no descontinuations.

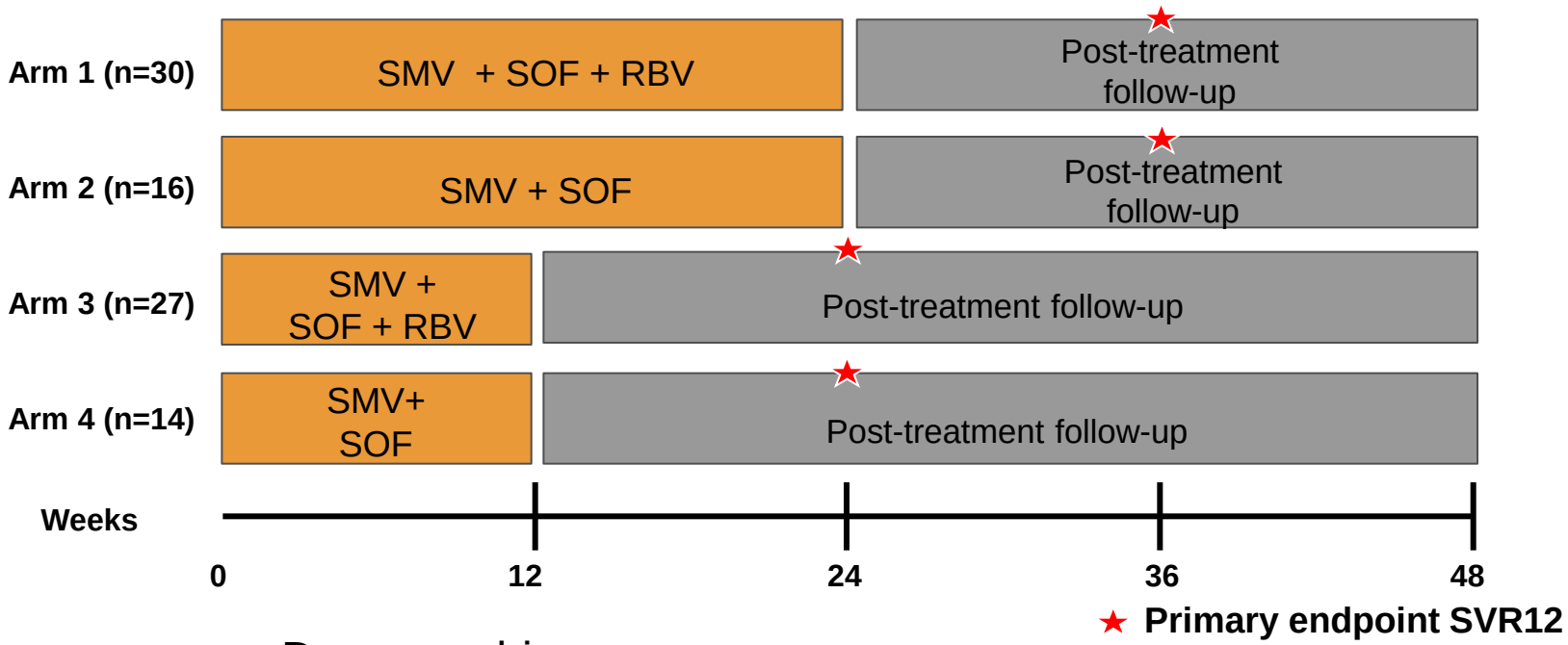
http://www.natap.org/2014/CROI/croi_110.htm

COSMOS (SMV+SOF±RBV)

SMV+SOF±RBV in HCV GT 1 Treatment Naïve and Prior Null Responders with F3–4 (Cohort 2)

‡

Phase 2, randomized, open-label study, stratified by ?



Demographics:

44-74% Male

3-19% African American; 10-31% Hispanic/Latino

Median Age: 57-58 yrs old

IL28B: non-CC: 71-88%

HCV Genotype 1a 75-82%

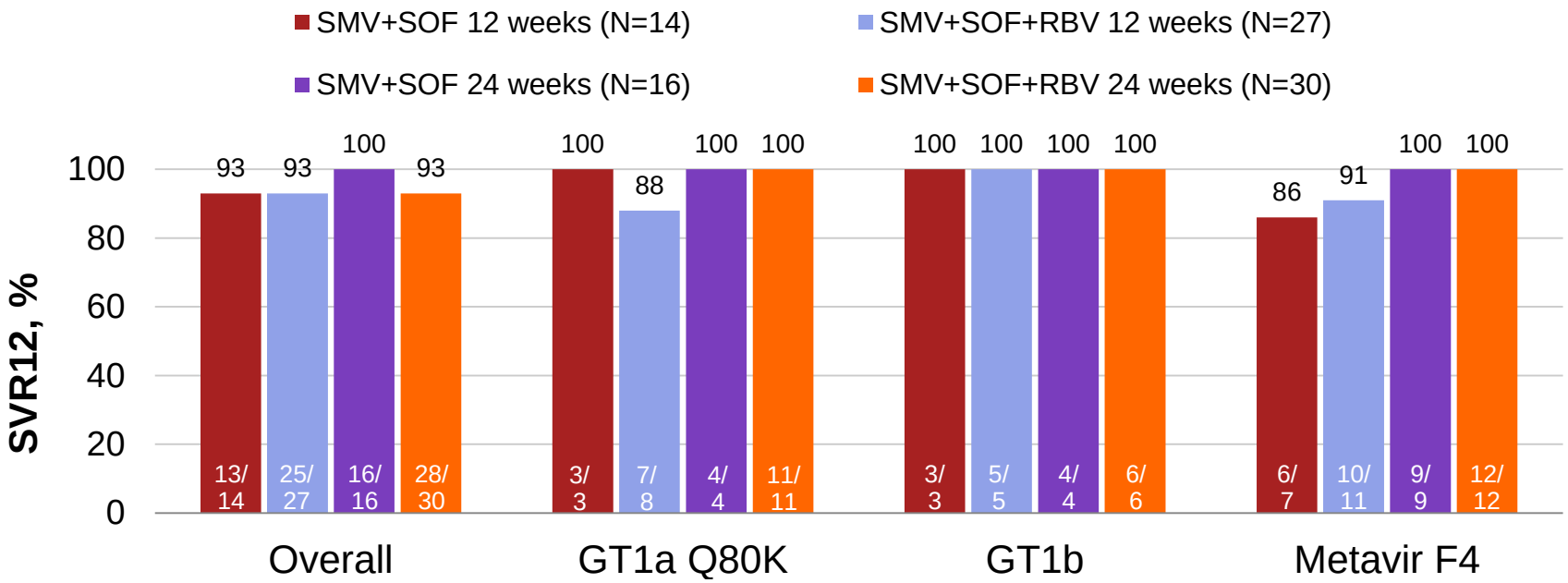
Median baseline viral load 6.3-6.7 $\log_{10}$

Cirrhosis by biopsy: 41-63%

Lawitz E EASL, 2014, O165
Clinical trials.gov: NCT01466790

‡

SVR12

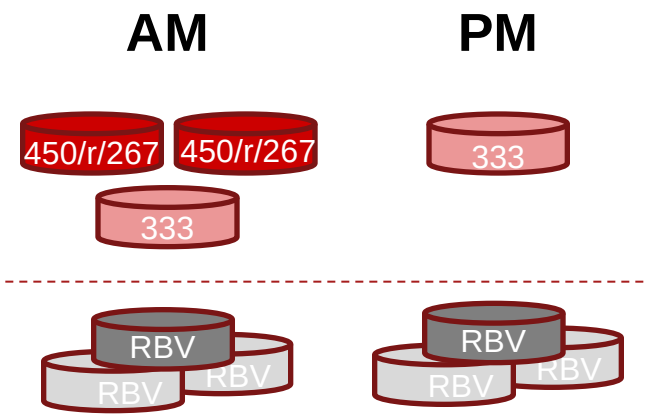


- No viral breakthrough
- Relapse occurred in 3 GT1a-infected patients
- Most common AEs: fatigue 37.9%, headache 19.5%
- Four serious AEs reported
- One patient D/C treatment due to AE

Lawitz E EASL, 2014, O165

AbbVie HCV Clinical Development Program
ABT-450/RTV/ABT-267+ABT-333±RBV in GT 1 Patients

Trial	Pt type	Treatment duration	SVR12	Virologic failure
SAPPHIRE-I	GT1, TN	12 wks	• 96% • GT1a – 95% • GT1b – 98%	• VBT 0.2% • Relapse 1.5%
SAPPHIRE-II	GT1, TE	12 wks	• 96% • GT1a – 96% • GT1b – 97%	• VBT 0% • Relapse 2.4%
PEARL-IV	GT1a, TN	12 wks	• 92% overall • 90% no RBV • 97% + RBV	• No RBV – 8% • + RBV – 2%
PEARL-III	GT1b, TN	12 wks	• 99% overall • 99% +/- RBV	• No RBV– none • + RBV: VBT 0.5%; relapse 0%
PEARL-II	GT1b, TE	12 wks	• 98% overall • 100% no RBV • 97% + RBV	• None
TURQUOISE-II	GT1 with compensated cirrhosis, TN, TE	12 or 24 wks	• 94% overall • 92% 12 wks • 96% 24 wks	• 12 wk : VBT 0.5%; relapse 5.9% • 24 wk : VBT 1.7%; relapse 0.6%



Target Profile

- FDC ABT-450/RTV/ABT-267 dosed QD (2 pills)
- ABT-333 dosed BID
- 12 week treatment duration for non-cirrhotic patients
- GT1a TN, GT1 TE, and cirrhotic patients require RBV in regimen

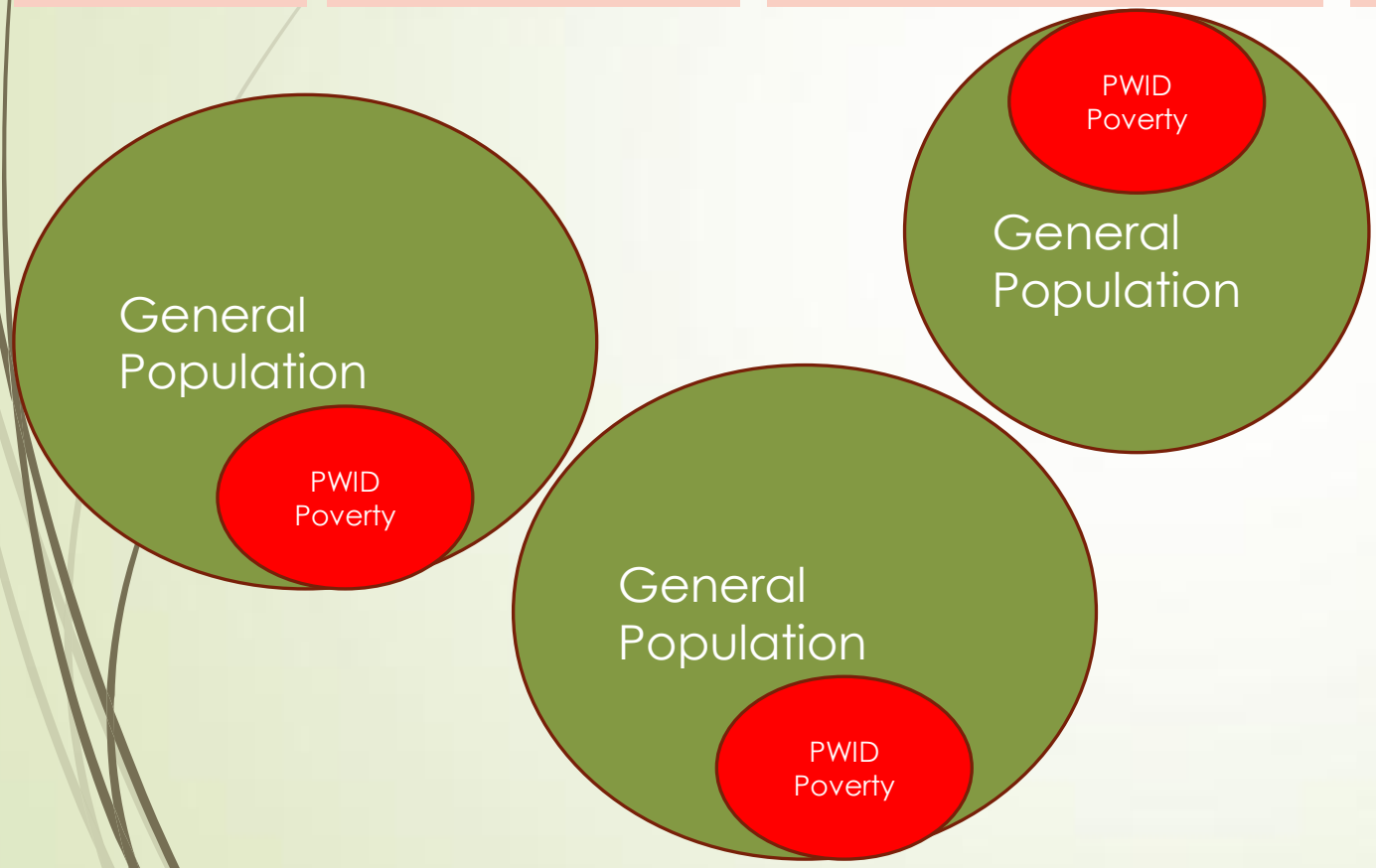
Probably possible to change….

An evolving landscape…

	Before 90's	90's: the IFN Era	2000's: the PegIFN Era	After 2012: the DAA Era
Acute Infection:	Expansion (high)	Expansion (high)	Lower Expansion (high selected sets)	Decrease (high selected sets)
Chronic Infection:	Expansion (high)	Expansion (high)	Expansion (high)	Stable (high/decrease)
Disease:	Expansion (modest)	Expansion (modest)	Expansion (high)	Expansion (high)
Death:	Low	Expansion (modest)	Expansion (high)	Expansion (high)
Cure:	Does it exists?	Low	Low/ Moderate	High but… access?

...and a race against the clock! Target populations are changing!

Before 90's | **90's: the IFN Era** | **2000's: the PegIFN Era** | **After 2012: the DAA Era** | **And beyond...**



How much eager to fight for the patients will the Society be?

Need a comprehensive policy NOW!

Science is almost all done! Now the challenge is to provide access(diagnostic and therapy)!

Science done! Now to become affordable

Editorial

Only just the beginning of the end of hepatitis C

2014 marks the 25th anniversary of the identification of the hepatitis C virus (HCV). HCV infection continues to be a major global health problem. Unlike many chronic diseases, hepatitis C can be cured, but it is difficult to treat, not all patients are responsive, side-effects can be severe, and progression to end-stage liver disease and liver cancer is common. Over the past few years, new medicines for HCV infection have begun to transform the treatment landscape, and, just in the past few months alone, the development of new regimens has been so successful that disease experts are heralding an era where all patients can be cured, even debating whether eradication is possible.

HCV has six major genotypes and the infecting genotype determines the treatment response and duration. Genotypes 1–3 have a worldwide distribution, but genotype 1 predominates in North America, Europe, and Japan, hence pharmaceutical research to treat this genotype has been preferred to others.

The new treatment modalities are once-daily oral combination regimens with optional inclusion of ribavirin and are pegylated interferon (peginterferon) free, so multiple tablets and injections are no longer needed. The novel agents are known as direct-acting antivirals (DAAs). In two phase 2 clinical trials published last week, the DAAs, sofosbuvir and daclatasvir, and the investigational DAAs, ABT-450, ABT-267, and ABT-333 in combination with known protease inhibitors, were shown to achieve high viral clearance response rates (83–100%) in previously treated and previously untreated patients with HCV genotype 1 with a short duration of therapy (12 weeks vs 48 weeks), together with a favourable safety profile compared with the current standard peginterferon based treatments.

Patients with HCV genotypes 2 and 3 also responded well to treatment and there was minimal need for clinical and laboratory monitoring. Testing of other promising DAAs is underway. Results are expected within the next 2 years. Rapid regulatory approval of sofosbuvir in the USA and Europe (and an expedited review of daclatasvir) have been accompanied by reports of promises from companies to ensure that access is achieved as quickly as possible. But given 90% of the estimated 184 million people with hepatitis C live in low-income and middle-income countries, how available and accessible will these new medicines be globally?

The main drawback of these new agents is the huge price tag, which will make treatment out of reach for people in the developed and developing world. Indeed, current treatment uptake is also impeded by cost. One 12 week course of sofosbuvir will cost US$84 000, even though the scientist involved in formulating sofosbuvir, Raymond Schinazi, estimates costs at just $1400. An even lower price was shown by Andrew Hill and colleagues in a recent study. Based on the fact that the new hepatitis C treatments are comparable in molecular structure and chemistry to HIV antiretrovirals, the authors used the same market dynamics to determine the minimum cost to manufacture them, which was $100–250 per 12 week treatment course; they concluded that at these low prices, widespread access to these new medicines is feasible within 15 years. Although manufacturers are likely to offer low-income countries steep discounts, around 75% of people with hepatitis C live in middle-income countries regarded as emerging markets by companies, and so are unlikely to benefit from the kind of discounts needed to make treatment available. Interestingly, the sofosbuvir patent application is currently under challenge in India, and if upheld will allow Indian generic drug companies to enter the market and drive major price reductions as seen with HIV/AIDS medicines.

The other concern is the limited testing of these new treatments on less common genotypes and marginalised populations disproportionately affected by HCV infection. For example, there has been minimal testing among those co-infected with HIV. Although the field is likely to see pan-genotypic treatments that clear all genotypes, and will also remove the need for a complex diagnostic, many countries are still years away from these scenarios.

The need for a global plan for hepatitis C is imperative. It should include research and operational priorities, and establish global funding mechanisms. Countries are only likely to develop national plans for hepatitis C when treatments become more affordable. Last year, Tido von Schoen-Angerer and colleagues in a *Lancet* letter rightly argued that UNITAID—which has successfully lowered prices of HIV treatments—should do the same for hepatitis C medicines. Lessons from HIV/AIDS will be instructive for the hepatitis C field, as will political and community mobilisation to ensure these treatments reach those in most need. ■ *The Lancet*

For more the **phase 2 trials** see *N Engl J Med* 2014; 370: 211–21 and *N Engl J Med* 2014; 370: 222–32

For the **study by Andrew Hill and colleagues** see http://hiv.oxfordjournals.org/content/early/2014/01/09/cid.ciu022.abstract

For the **letter on UNITAID** see Correspondence *Lancet* 2013; 381: 628

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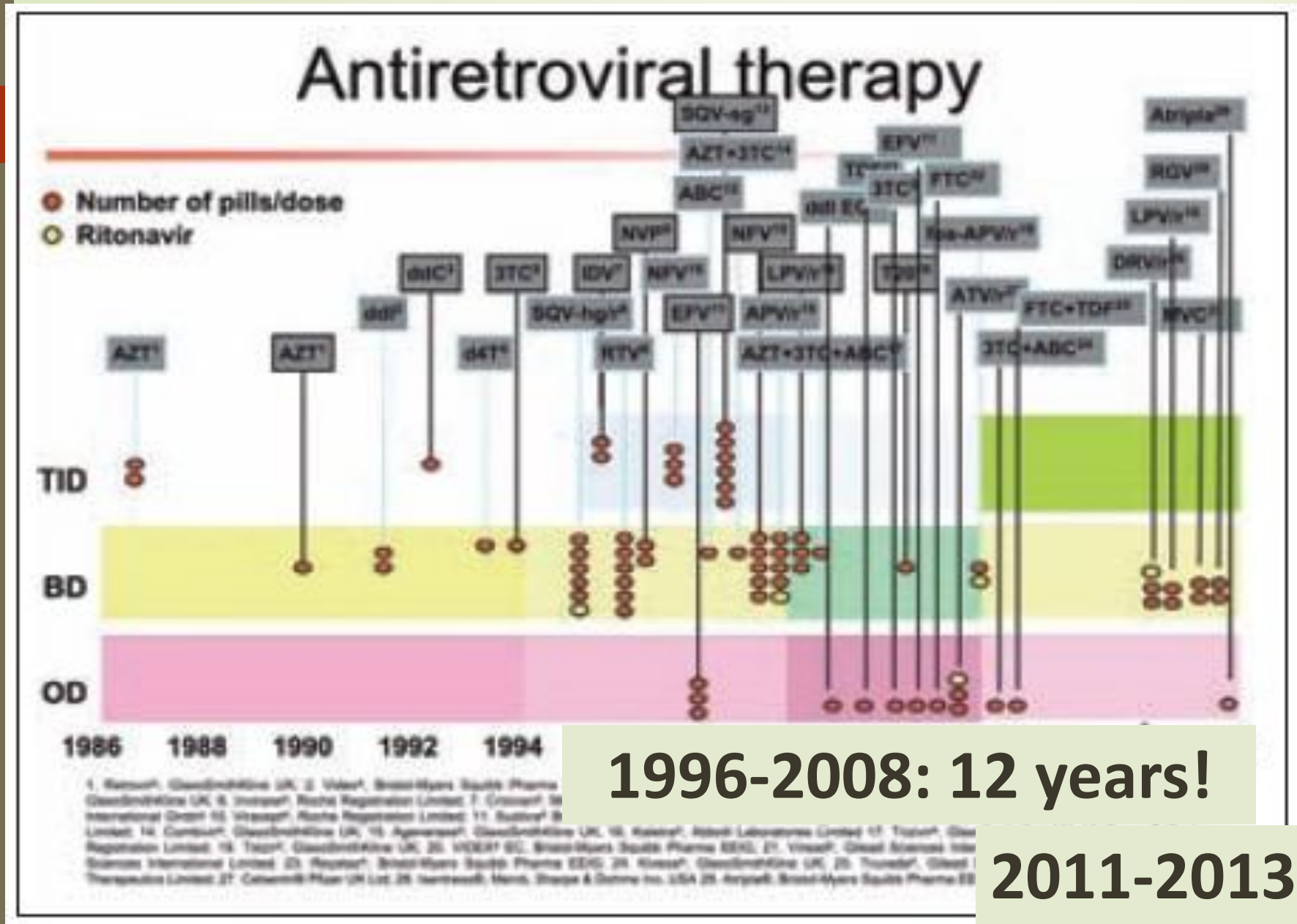


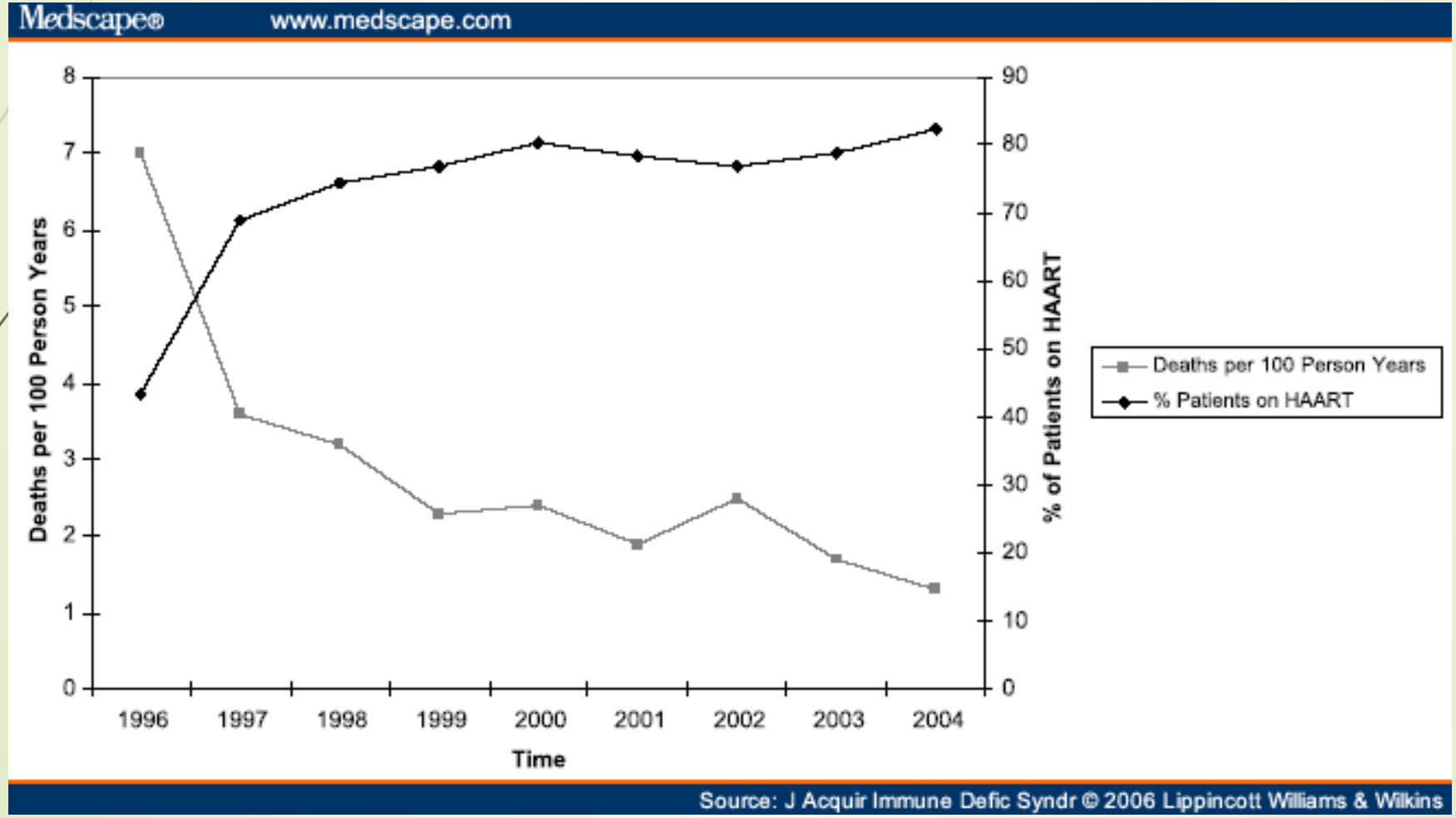
We learn a lot with ART Development!

1996-2008: 12 years!

HCV

2011-2013: 2 years from PI 1 to PI 2 + NUC (SOF)!

Dramatic shift on HIV related death rate after HAART.



An evolving landscape

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An evolving landscape

Access

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Cure:	Does it exists?	Low	Low/ Moderate	High

An ideal landscape (access): a new beggining!

	After 2012: the DAA Era	2014 & beyond: DAA Era & IFN free
Acute Infection:	Decrease (high selected sets)	Decrease (high selected sets) Vaccine?
Chronic Infection:	Stable (decrease)	Decrease
Disease:	Stable (decrease	Decrease
Death:	Decrease	Decrease
Cure:	High	High

Science is almost all done!
Now the challenge is to provide access (diagnostic and therapy)…
and simplicity!

Access to diagnosis and therapy plus simplicity = opportunities and inclusion

Today: the disease

- Treat "ill" people ie "F2", F3 and F4
- But not so ill: advanced disease, comorbidities, elderly people
  - Excluded: HIV-HCV, incarcereted, PWID, homelless, comorbidities, certain genotypes and previous non responders
- HAVE TO HAVE: several and complicated laboratory and other diagnostics tools, a place to treat, a team approach, a hospital to go (ie: side effects), other drugs to treat side effects and a huge budget

Soon: the infection

- Treat "infected" people
- Treat all*: mild to severe, single to multiple diseases
- Inclusion will be the rule: HIV-HCV, incarcereted**, PWID**, homelless, comorbidities, pangenotype and previous failures
- HAVE TO HAVE: simple tools (point of care), an average clinic, compliance and, still, a huge budget (or not: **State policies, affordable drugs and partnerships**)

* Potentially all

** Opportunity to do **DOT**!!!!

Simplifying the model of care

- International guidelines (including for resource constrained settings)

- Low cost/technology diagnostics
  - Point of care antibody testing
  - Dried blood spots for HCV RNA testing

- Expansion of non-invasive disease staging

Adapted from Mehta SH, 2014

And simplifying the medical care

World Health Organization

GUIDELINES FOR THE SCREENING, CARE AND TREATMENT OF PERSONS WITH HEPATITIS C INFECTION

APRIL 2014

7.5 Treatment with sofosbuvir

Sofosbuvir, given in combination with ribavirin with or without pegylated interferon (depending on the HCV genotype), is recommended in genotypes 1, 2, 3 and 4 HCV infection rather than pegylated interferon and ribavirin alone (or no treatment for persons who cannot tolerate interferon).

Strong recommendation, high quality of evidence. This recommendation was made without taking resource use into consideration, as pricing information was not available for any country other than the United States at the time this recommendation was formulated.

7.6 Treatment with simeprevir

Simeprevir, given in combination with pegylated interferon and ribavirin, is recommended for persons with HCV genotype 1b infection and for persons with HCV genotype 1a infection without the Q80K polymorphism rather than pegylated interferon and ribavirin alone.

Strong recommendation, high quality of evidence. This recommendation was made without taking resource use into consideration, as pricing information was not available for any country other than the United States at the time this recommendation was formulated.

EASL, IDSA, Veteranos EUA

AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

AASLD

IDSA
Infectious Diseases Society of America

The most current version of the HCV Guidance exists on *Recommendations for Testing, Managing, and Treating Hepatitis C*. (http://www.hcvguidelines.org)

Home > INITIAL TREATMENT OF HCV INFECTION IN PATIENTS STARTING TREATMENT

INITIAL TREATMENT OF HCV INFECTION IN PATIENTS STARTING TREATMENT

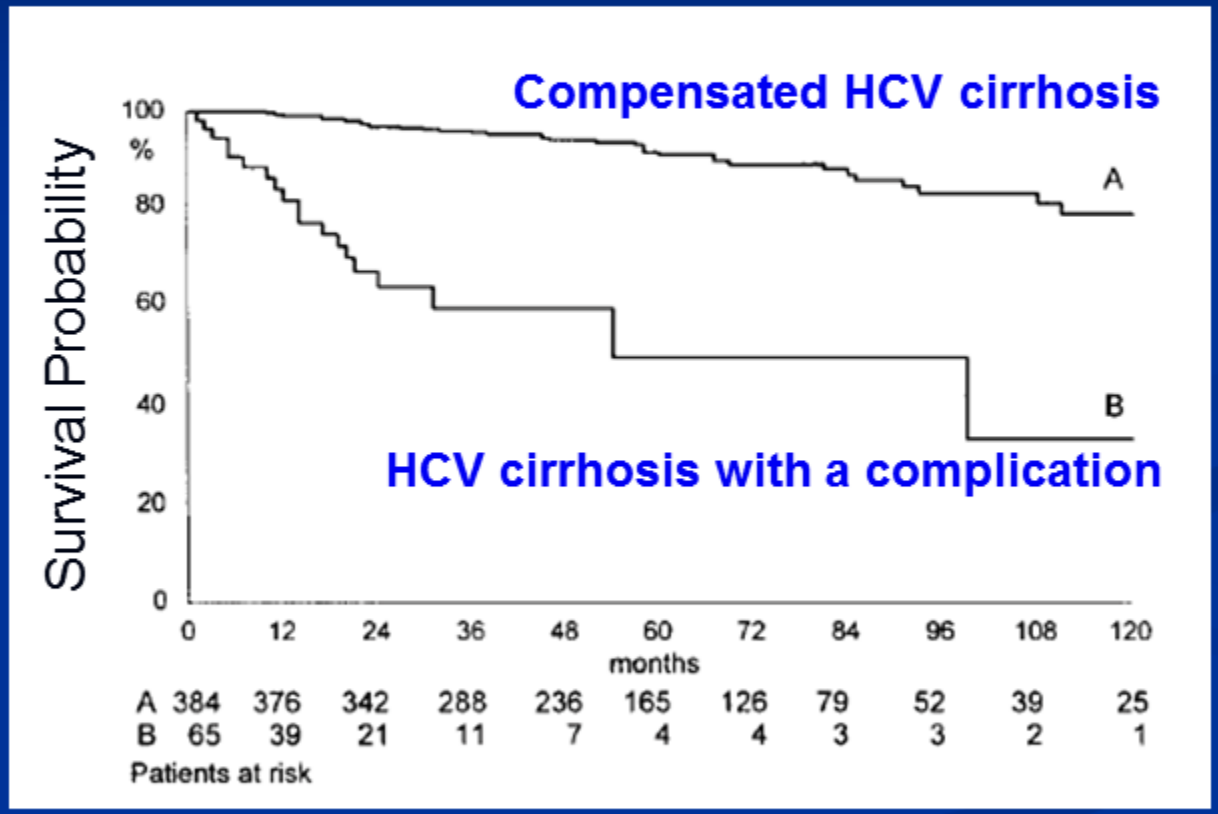
Chronic Hepatitis C Virus (HCV) Infection:
Treatment Considerations from the Department of Veterans Affairs National Hepatitis C Resource Center Program and the Office of Public Health
(March 27, 2014; data last reviewed on March 6, 2014)

Novo cenário!

Crossroad

- This is no longer a simple medical decision: this is too heavy to be on our shoulders
- IFN based (and even PI first generation): by far inadequated
- IFN free: still beggining but much better
- Pragmatic vs Need to treat
- How to not become a "companie's hostage"
- Using (in favor) the Natural History of disease
  - Not all patients need to be treated "now"

Good short-term survival with compensated cirrhosis



91% 5-year and 79% 10-year survival in Child's A cirrhosis (ie. most compensated patients can actually wait…)

Fattovich et al Gastro 1997

Key Actors

- Government (MOH)
- WHO & Brazilian new WHO resolution
- Pharmaceutical and Diagnostics Companies
- NGO & Advocacy (including official)
- Scientific Societies
- Media

Manufactoring an immunobiologic agent

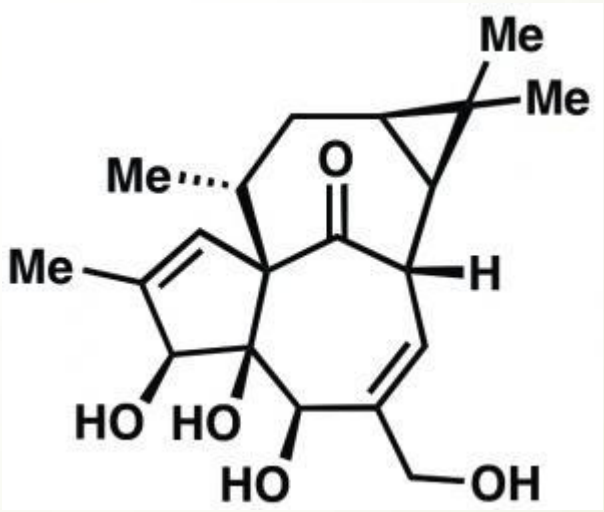
Sometimes works.....

Sometimes not!

Difficult to obtain a good generic agent

Manufactoring an antiviral agent

Always works.....



Need to push for generic agents or fair prices!

What we learned with HIV drugs?

Advocacy plus....

Generics!

We don't need to be a hostage to the Market anymore!

Unlimited profits!

Partnership is better!

NIH National Institutes of Health
Turning Discovery Into Health

Accelerating Medicines Partnership

The Accelerating Medicines Partnership (AMP) is a bold new venture between the National Institutes of Health (NIH), 10 biopharmaceutical companies and several non-profit organizations to transform the current model for developing new diagnostics and treatments by jointly identifying and validating promising biological targets of disease. AMP will begin with three to five year pilot projects in three

http://www.nih.gov/science/amp/index.htm

Brazil is doing what have to do!

PORTARIA CONJUNTA Nº 1, DE 5 DE MARÇO DE 2014

Institui o Comitê Interinstitucional para Acompanhamento das Ações Estratégicas

de DST, Aids e Hepatites Virais, no âmbito do Ministerio da Saúde e Agência Nacional de Vigilância Sanitária.

Art. 1º Fica instituído o Comitê Interinstitucional para Acompanhamento das Ações Estratégicas de DST, Aids e Hepatites Virais para promover ações articuladas entre entes do Sistema de Vigilância em Saúde.

Art. 2º Compete ao Comitê:

I - acompanhar sistematicamente o plano estratégico de implantação dos insumos estratégicos relacionados às DST, aids e hepatites virais;

II - discutir tecnicamente a incorporação de novas tecnologias para prevenção, diagnóstico e tratamento das DST, aids e hepatites virais; e

After starting IFN free Era

Epidemiology

- Potential to a dramatic change
- Harm Reduction: key to avoid reinfection among selected people
- Vaccine: still necessary among selected people (PWID, poverty)

Burden

- Potential to a dramatic change
- Less deaths and complications
- Need to have a Global approach to avoid/minimize therapy exclusions and preventable infections/reinfections

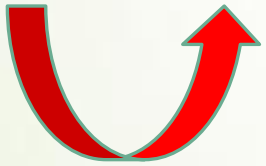
We saw that before: a changing scenario and a new way to think!

- **HIV: lethal disease to a chronic disease with functional "cure"**
- **HCV: chronic and potencially lethal disease to a curable infection**
  - **Therapy as dual prevention: infection & disease**
- **Not only a therapeutic change but an entire new approach and act plan!!!!!**

Conjuntura da Terapia da Hepatite C

Terapia Atual	Terapia Futura (≥ 2014)	
↓Efetividade ↑Efeitos Colaterais Difícil ingesta (adesão ruim)	↑Efetividade ↓Efeitos Colaterais Fácil ingesta (adesão facilitada)	✓ Coinfecção HIV ✓ IFN intolerantes ✓ PWID/Encarcerados ✓ Pré-Pós-Transplante
$$	$$$ X $$$	

Problema 1: Custo!!!!!!



Negociação

- $$ - possibilidade de ≤ gasto atual com a terapia vigente (minimizar/eliminar impacto orçamentário – mesmo dinheiro!)

Problema 2: Anvisa!!!!!!

- Priorizar (Ação Política & Estratégica!!)
  NÃO é indicação da "Indústria":AASLD, EASL e **OMS**!
- Pactuar ONG/Soc.Científicas/Legislativo/Farma
  Reconhecer que o *warehousing* ocorre

David Capistrano teached us the correct questions:

( )“Is it possible?”

( ) HOW TO MAKE IT HAPPEN?

David Capistrano teached us the correct questions:

( )"Is it possible?"

(**X**) HOW TO MAKE IT HAPPEN?

Few weeks after the 1996 Vancouver Conference the first city in Brazil (before the country!) to buy 200 therapies for public patients was Santos, in where he was the mayor.

Once you choose

HOPE, anything's possible.

- Christopher Reeve

Everything new: deal with the burden (liver disease) and modify epidemiology (treat infection)!

Thank you for your attention!